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Minireview

Natural and abrupt involution of the mammary gland affects differently the metabolic and health consequences of weaning

Nissim Silanikove *

Biology of Lactation Lab., Institute of Animal Science, Agricultural Research Organization (ARO), PO Box 6, Bet Dagan 50250, Israel

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ABSTRACT

In most mammals under natural conditions weaning is gradual. Weaning occurs after the mammary gland naturally produces much less milk than it did at peak and established lactation. Involution occurs following the cessation of milk evacuation from the mammary glands. The abrupt termination of the evacuation of milk from the mammary gland at peak and established lactation induces abrupt involution. Evidence on mice has shown that during abrupt involution, mammary gland utilizes some of the same tissue remodeling programs that are activated during wound healing. These results led to the proposition of the "involution hypothesis". According to the involution hypothesis, involution is associated with increased risk for developing breast cancer. However, the involution hypothesis is challenged by the metabolic and immunological events that characterize the involution process that follows gradual weaning. It has been shown that gradual weaning is associated with pre-adaption to the forthcoming break between dam and offspring and is followed by an orderly reprogramming of the mammary gland tissue. As discussed herein, such response may actually protect the mammary glands against the development of breast cancer and thus, may explain the protective effect of extended breastfeeding. On the other hand, the termination of breastfeeding during the first 6 months of lactation is likely associated with an abrupt involution and thus with an increased risk for developing breast cancer. Review of the literature on the epidemiology of breast cancer principally supports those conclusions.

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Introduction

The development of the mammary gland secretory tissue occurs mostly at the end of pregnancy (Capuco and Akers, 1999; Lund et al., 1996). In most freely behavior mammals, including humans (Neville et al., 1991), mice (Quarrie et al., 1996) and ruminants (Capuco and Akers, 1999) involution occurs following the cessation of suckling by the offspring. Involution is the process whereby redundant mammary epithelial cells (MEC) are removed, which is one of the most notable examples of physiologically regulated cell death in an adult tissue (Capuco and Akers, 1999; Lund et al., 1996). Usually, involution occurs at the declining part of lactation where suckling rate and milk secretion are at their lowest levels and the offspring already partially consumes post-weaning food. Natural weaning (NW) is influenced by

* Tel.: +972 8 9484436.
E-mail address: Nissim.silanikove@mail.huji.ac.il.

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circumstantial events that occur along the lactation such as, disease of the offspring or dam, rate of non-milk food consumption, etc. Weaning is therefore usually scattered within extended time interval, even in a group of humans or animals that gave birth at about the same time. Conducting an experiment, however, requires similarity among the test groups; particularly toward the assessed biological hypothesize. To overcome this difficulty, involution is induced abruptly at the beginning of lactations. At this stage, individual differences between the dams are still small. The majority of the information about developmental, metabolic and immunological outcomes of involution in farm (Capuco and Akers, 1999) and experimental animals (Faupel-Badger et al., 2013) are based on implying early-lactation-forced-involution (ELFI) procedures. ELFI procedures comprised: teat sealing (Li et al., 1997), unilateral cessation of milking of single gland (Quarrie et al., 1994), abrupt removal of youngs, or complete cessation of milking (Shamay et al., 2002). However, there is no evidence to support the inherent assumption; namely,the outcome of ELFI procedures that essentially reflects metabolic and immune result of NW.

The first stage of involution (stage I), which covers the events occurring between the induction of milk stasis and extensive degradation of the secretory tissues (stage II),associates with the widespread apoptosis of the alveolar epithelial cells (Lund et al., 1996). Evidence based on ELFI procedures in mice has shown that during involution the mammary gland (MG) utilizes tissue remodeling programs that are activated during wound healing (Clarkson et al., 2004; Stein et al., 2004). Specifically, the amplification of set of gens typical to those aroused during wound healing at the very first phase of involution (12 h) was found to be associated with immune cell infiltration and short-term formation of wound healing matrix components (Clarkson et al., 2004; Stein et al., 2004). Because similar changes confer a risk for developing cancer, it was suggested that MG involution *per se* may represent a window of opportunity for tumor cell progression (Clarkson et al., 2004; Lyons et al., 2011; Maller et al., 2010; McDaniel et al., 2006; O'Brien et al., 2010; Schedin et al., 2004; Stein et al., 2004). This theory was coined by a panel of experts that reviewed the relationships among postpartum remodeling, lactation, and breast cancer as the "involution hypothesis" (Faupel-Badger et al., 2013). Thus, the question whether MG involution induced by ELFI procedures resemble the process followed by NW becomes critically important, particularly, from human health perspective. Similar thought was expressed by the above-mentioned panel of experts (Faupel-Badger et al., 2013).

The challenging data

A recent study in dairy cows has shown that involution induced under conditions that resembled NW, behaved like an orderly tissue remodeling programs. The involution under NW-like conditions was associated with effective clearing of apoptotic cells and produces conditions for eradicating or preventing new bacterial infections (Silanikove et al., 2013). On the other hand, involution in cows under forced weaning (FW)-like situation resembled the involution induced by ELFI procedures in mice. As in mice, FW-like involution was associated with distressed wound-healing like response (Silanikove et al., 2013). The involution under FW-like conditions was associated with inferior ability to prevent bacterial invasion into the mammary gland. In the rest of the overview, scientific literature is critically evaluated in order to substantiate the concept that involution induced under NW and FW is fundamentally different from each other.

What is the basic difference between natural and abrupt involution?

Mammary gland involution can be induced at each stage of lactation, even at the very beginning of lactation and during the peak of milk yield, by inducing milk stasis. The unilateral cessation of milking in goats (Quarrie et al., 1994), and teat sealing in mice (Li et al., 1997) induced involution only in the treated gland. This specific response indicates that mammary involution is triggered by local milk-born stimuli. Several proposals for explaining the mechanism behind the negative feed-back regulation of milk secretion were proposed (Pai and Horseman, 2008; Quaglino et al., 2009; Silanikove et al., 2005, 2006). However, it seems that much more remained to be delineated in order to understand the physiological basis that underlies this feed-back process.

Involution in NW-like cows was associated with metabolic and immunological adaptations toward the expected disconnection between dams and their offspring, which was interpreted as an auto-defense mechanism (Silanikove et al., 2013). The large scale of cell apoptosis that characterizes MG involution stage I requires an effective clearance of the dead cells to avoid necrosis and uncontrolled inflammation. The metabolic and immunological adaptations in NW-like cows allowed MG involution to proceed as an orderly tissue remodeling programs (Silanikove et al., 2013).

The first conspicuous phenological feature of NW-like and FW-like involution is the disruption of the tight junctions (TJ) between MEC (Silanikove et al., 2013). When mammary gland involution was induced in nonadapted (FW) cows, the response was associated with neutrophilia and lymphopenia and resembled the general response to wounding (silanikove et al., 2013). The large influx of neutrophils to the MG was regarded as a response to urgent situation. The neutrophils serve as 'gate keepers' of the open TJ in order to prevent life threatening bacteremia (penetration of bacteria from the gland lumen to the blood system) and penetration of milk proteins such as, casein and casein derived peptides (McFadden et al., 1988), which can induce uncontrolled inflammation (sepsis) in the blood (Metcalf et al., 1996; Silanikove et al., 2013).

In NW-like involution, total disruption of the TJ was preceded by a partial disruption. The partial opening of the TJ is important for developing auto-defense responses. The pre-involution opening of the TJ in NW cows was associated with inflammatory response. However, the inflammatory response in NW-like cows was distinctively different from the acute response observed in cows undergoing FW-like involution: it was characterized by a balance presentation among neutrophils, T-cells (CD^4 and CD^8 subtypes) and macrophages in the gland lumen (Silanikove et al., 2013). The above-described response most likely prevents the stress caused by the sudden total disruption of the TJ.

To which extent the findings in non-human species are relevant to human?

Mice serve as the prevailing experimental model for evaluating biological questions important for human where direct experiments are not possible, or ethical (e.g., Vanhooren and Libert, 2013). Mice are small, cheap and have short reproductive cycle and life span, whichmake them convenient model for testing biological concepts. However, models on inflammation and immune response based on experiment with mice were shown time and again not to precisely predict behavior in human beings (Cauwelsa et al., 2013; Osterburg et al., 2013; Seok et al., 2013). Experimental results from the given mammalian species may be used to build useful conceptual models relevant to different species, if it helps to generate testable hypotheses for ultimate verification in the target species. From this viewpoint, it is considered useful to exploit the extensive information on the biology of lactation in farm animals. Some of the biological features of farm animals, such as pregnancy and lactation cycle length and the rate of involution in cows are more similar to human than those of mice. In comparison to the mammary glands of mice and rats, which can resorb milk components entirely and complete involution within approximately 7 days (Lund et al., 1996), the involuting gland of women remained functional for a long period, with secretion still being present in the lumen of the MG for up to 42 days after the abrupt termination of breast feeding (Hartmann and Kulski, 1978). The involution process in FW-like cows